PHACE Syndrome: Persistent Fetal Vascular Anomalies

A Case Report

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Summary

PHACE(S) syndrome is an acronym for neurocutaneous disease encompassing the expression of (P) posterior cranial fossa malformations, (H) facial haemangiomas, (A) arterial anomalies, (C) aortic coarctaion and other cardiac defects, (E) eye abnormalities and (S) for sternal malformation or stenotic arterial diseases. We report on a case of PHACE syndrome complete expression with persistent fetal vascular anomalies unusually in a 55-year-old women with large bilateral facial and neck haemangioma and posterior fossa circulation insufficiency.

Introduction

The cephalic neural crest provides pericytes and smooth muscle cells to all blood vessels of the face and forebrain and has been implicated in the pathogenesis of the PHACE(S) syndrome [1]. Recent advances in developmental biology have shown links between neural crest lesions prior to the fourth week and cephalic mesoderm anomalies in development. Haemangiomas with vascular anomalies and congenital heart diseases have been reported to be associated in complex developmental disease PHACE syndrome proposed as an acronym by Frieden et Al. in 1996. Haemangiomas, localized tumors of blood vessels, appear in 10-12% of caucasian infants. These lesions are characterized by a rapid proliferation of capillaries for the first year proliferating phase, followed by an involuting phase of one to five years. Haemangiomas have been also associated with Dandy–Walker syndrome and recently Bhattacharya put forward new explanations for and classification of the Wyburn-Mason syndrome, suggesting lesions of the neural crest and possibly the cephalic mesoderm [2].

Patient Characteristics

A 55-year-old woman was addmitted to hospital with a 12 hour history of visual disturbances accompanied by vertigo, nausea without vomiting, right-sided extremity paresthesias and occipital area pain. Symptoms recurred the next day for the same time period. Recent hypertension was treated with betablockers and CT scan for the posterior fossa led to a suspicion of TIA. The initial CT scan confirmed right PcomA- ICA aneurysm with ICA calcifications. The patient was transferred to our hospital for a 3D-XRA diagnostic angiogram for potential embolization treatment.

Description of Diagnostic Techniques

DSA - 3D-XRA four vessel angiogram was done using a GE-LCV+ combo system. A 5F Terumo (Radiofocus, Tokyo, Japan) sheath was introduced into the right common femoral

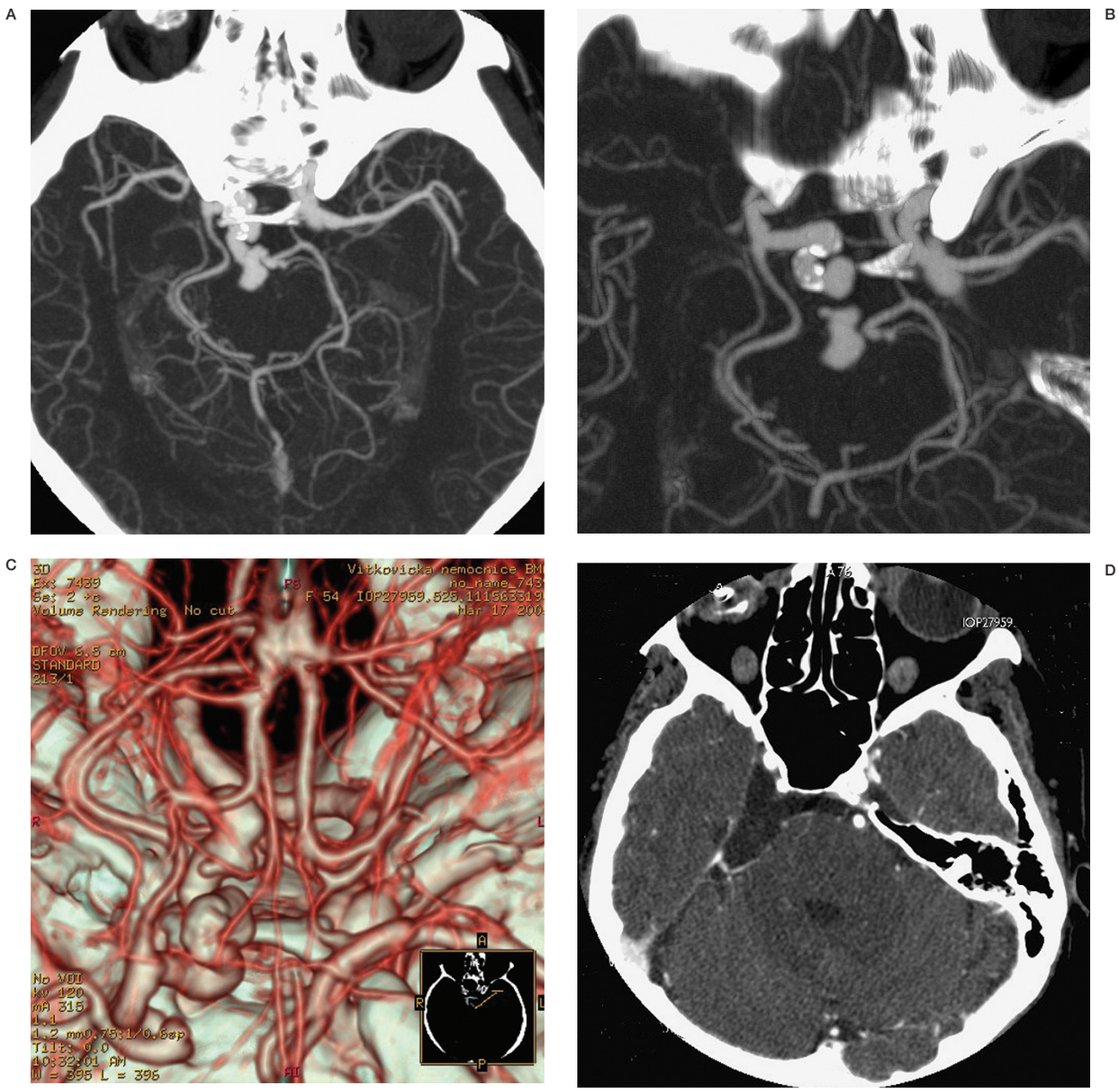


Figure 1 A,B) CTA MIP projections with calcified right PcomA with aneurysm. C) CTA VRT reconstructions with malformed C1 right supraclinoid segment, agenesis of the precommunicating right A1 segment. D) CTA source pictures- communicating arachnoid cyst at the right pyramind apex right pontocerebellar angle.

artery, 5000 units of UF heparin were administered intraarterially and the intial aortic-arch angiogram was finalized by the 4F Vertebral Aqua - Tempo catheter (Cordis - Endovascular, JJ, Miami, FL). The result showed complete right sided aortic arch without the inverted heart position, coarctation of the aortic arch below the origin of the left subclavian artery in loco typico (figure 2). Due to the anatomic abnormalities in the ascending aorta another 4F Simons 1- Aqua - Tempo catheter (Cordis - Endovascular, JJ, Miami, FL) was established and selective right subclavian artery (SA) angiography was performed. Dominant right vertebral artery (VA) with right posterior communicating artery (PcomA) dilatation and the C2-right internal carotid artery (ICA) segment with the right middle cerebral artery (MCA) filling was demonstrated. An aneurysm of the right PcomA was sustained by 3D-XRA reconstruction

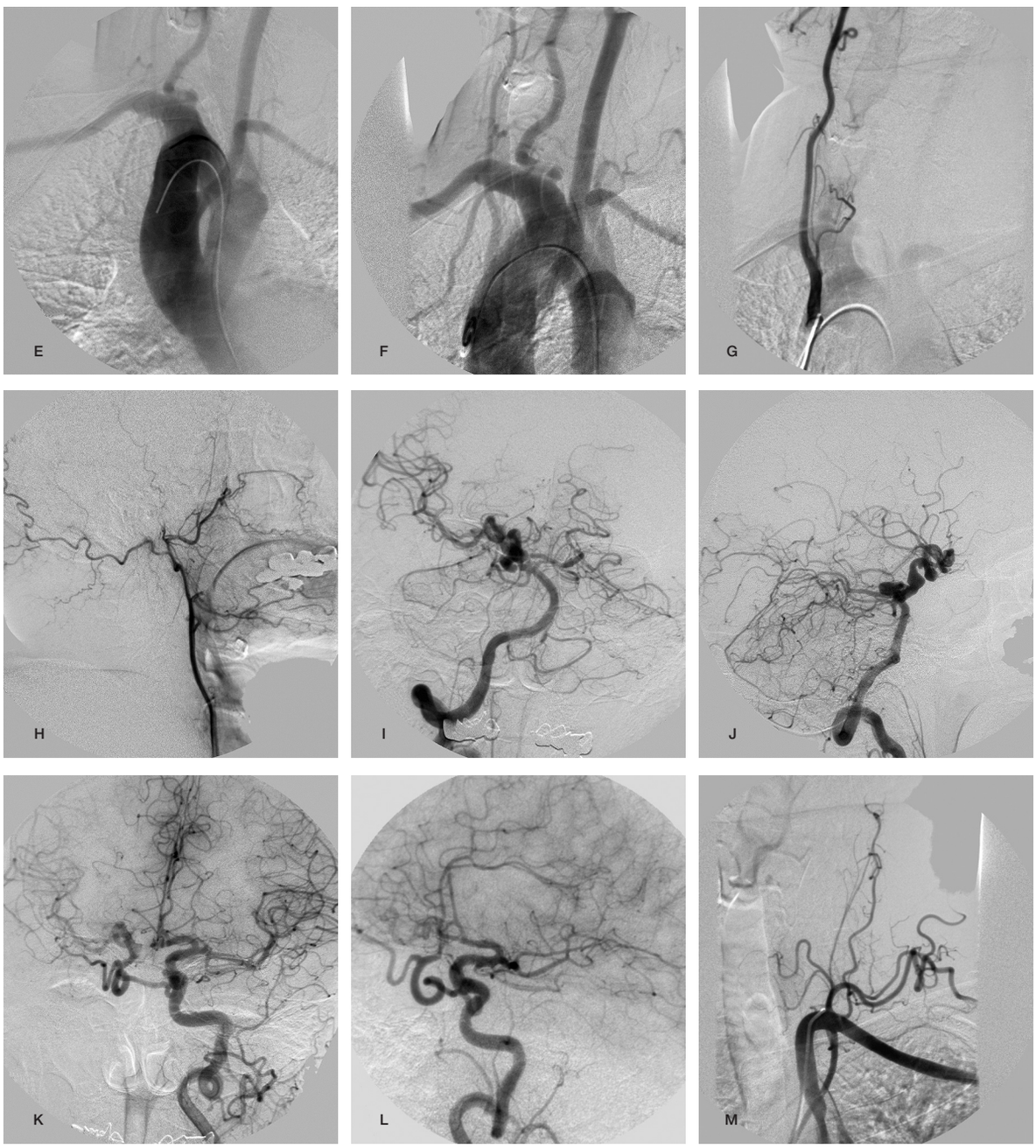
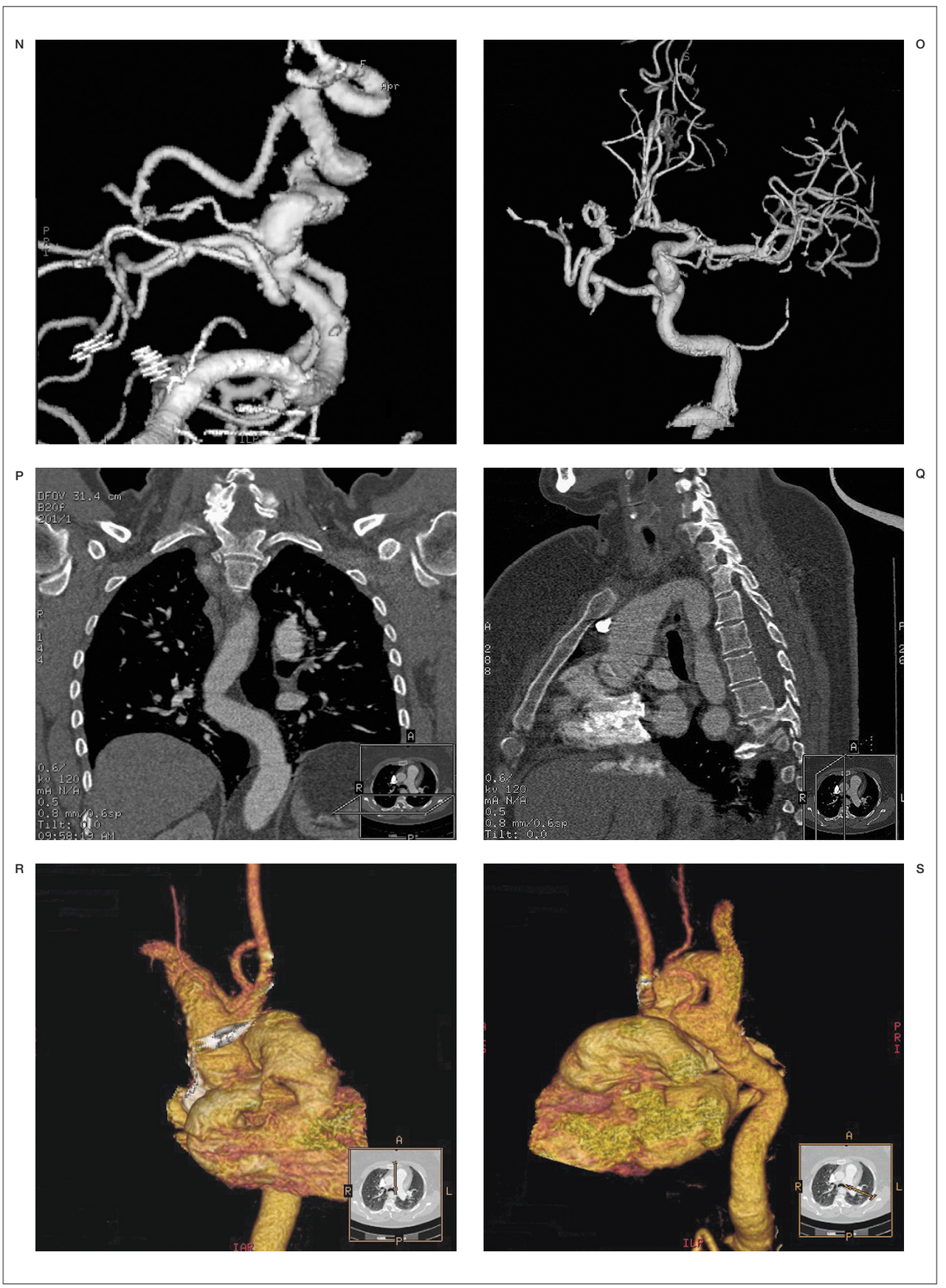


Figure 2 E,F) Inverted aortic arch with agenesis of the right ICA, ascending aorta origin of the right ascending cervical artery, left CCA and robust origin of the right SA. Aortic coarctation in loco typico. G,H) Right ascending cervical artery atypical fetal origin from the first right intercostal artery of the ascending aorta and supplying the right ECA territory. I,J) Right VA filling the supraclinoidal C1-right ICA segment through the right PcomA with the dominant right MCA supply. K,L) Persistent primitive maxillary artery with the cross-filling of the right ICA cavernous portion. Agenesis of the right A1precommunicating segment. M) Agenesis of the left VA.

(figure 3). The initial aortic arch angiogram surprisingly confirmed the right common carotid artery (CCA) and internal carotid artery agenesis in the extracranial cervical level. The area of the right external carotid artery (ECA) was substantialy supplied by the ascending cervical artery with atypical persitent fetal origin from the first right intercostal artery (figure 2-G,H).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Left CCA atypically originated as the first vessel deeply from the medial wall of the ascending aorta. Left ICA reconstructed in the 3D-XRA angiogram showed a persistent primitive maxillary artery with the filling of the C3–C4 right ICA cavernous intracranial portion and the right ophthalmic artery. (figure 2K,L, figure 3O) Agenesis of the right A1- anterior cerebral artery (ACA) precommunicating segment was acknowledged (also visible on the CTA- VRT reconstruction). Selective left SA angiogram confirmed agenesis of the left VA (figure 2M).

After completion of the diagnostic angiogram, we were facing a patient with the large bilateral extensive face and neck haemangioma, large vessel anomalies, aortic arch coarctation, common carotid artery and internal carotid artery agenesis, intracranial aneurysm and persistent primitive fetal maxillary artery. The PHACE(S) syndrome was suspected and therefore CT-angiogram of the heart, aortic arch and the brain folowed by a transesophageal echocardiography (TEE) was subsequently completed.

CT-angiography verified not only the angiographic situation and the calcifications of the right PcomA-ICA with the aneurysm 6 x 6.8 mm in diameter. An arachnoid cyst 9mm in diameter at the right pyramid apex and pontocerebellar angle was discovered. These also belong to the posterior fossa malformations in the PHACE(S) syndrome. The angioarchitecture of the aortic arch was afterwards reconstructed and the aortic coarctation measured. CT-perfusion showed symmetrical cortical cerebral blood volume (CBV) and cerebral blood flow (CBF). Slight asymmetry in the time to peak (TTP) reconstruction which is compatible with right ICA agenesis and collateral flow through the right PcomA was detected.

We also mentioned the ventricular septal defect in the sagittal scans, which was subsequently confirmed by the Transesophageal echocardiography (TEE) (figure 4). TEE was done by Ge-Vivid 7 ultrasound equipment with a 2 MHz TEE probe. Aortic root diameter measured 3.7 cm with tricuspidal aortic valve, left ventricular LVD- 4.8/2.5 cm diastolic and systolic diameters, ejection fraction EF-80%, right atrium 4.8 x 5.6 cm, right ventricule 4.1 cm and ventricular septal defect in pars membranacea with the pulmonary artery dilatation 3.5 cm. Ventricular septal defect with the left-to-right shunt was then calculated by Qp/Qs= 324/118.

Nuclear bolus radiography for the left to right shunt quantification with sequential scintigrams of bolus recirculation showed a small L-R shunt Qp/Qs = 1.15 without any pathological changes in central haemodynamics.

ECG showed sinus rhythm of 58beats/p.m., horizontal axis, PQ interval 0.20 QRS 0.08 RSR in V1-V4, negative T wave in III,V1, ST segments isoelectric without any ischemic signs. Incomplete right bundle branch block was visible. No changes in left ventricle hypertrophy were visible.

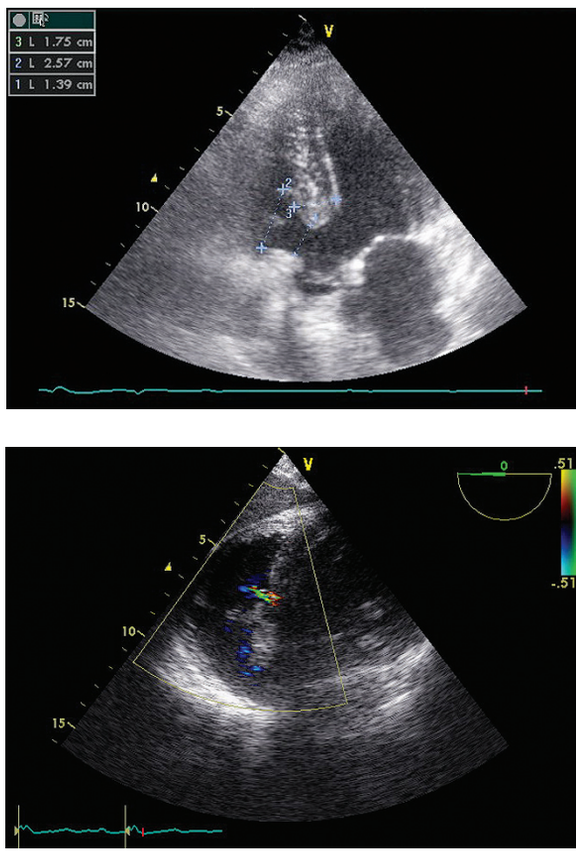

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Figure 4 T) Transesophageal echocardiography with congenital ventricular septal defect and CBF and CBV symmetrical cortical filling.

Figure 3 N) 3D-XRA right VA reconstruction with PcomA aneurysm. O) 3D-XRA left CAG reconstruction with primitive maxillary artery and the right C3 ICA segment with ophthalmic artery filling. P,Q) Thoracic aorta CTA MIP right sided aortic arch with coarctaion in loco typico. R,S) Thoracic aorta CTA VRT left CCA and right ascending cervical artery origin from ascending thoracic aorta.

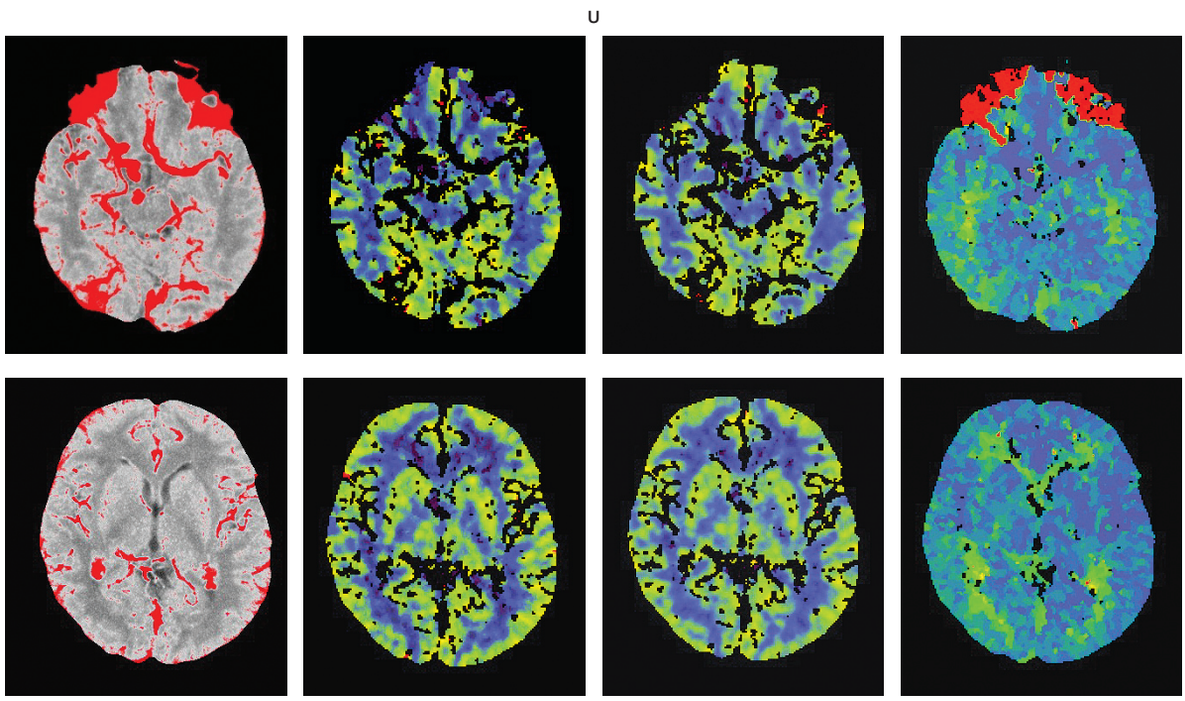

Figure 4 U) CTP-perfusion in two slices with right hemisphere asymetry in TTP-time to peak. In CBF and CBV symetrical cortical filling.

Brain MRI in PTD, T1 axial RISE, T1,T2-sagittal and coronal scans depicted the right eye bulb phthysis with optical nerve atrophy, which is also very important for the PHACE(S) syndrome complex.

The patient was put on conservative antihypertensive treatment and blood pressure subsequently returned to normal levels. No indication for asymptomatic aneurysm embolization was decided due to the vessel wall morphology with calcifications and the etiopathology of vascular anomalies. Heart function follow-up due to the left-to-right shunt was scheduled at six-month intervals.

Discussion

The first clinical report on the association of cervicofacial haemangiomas with vascular and intracranial malformations was made by the

Table 1 **Patients - PHACE syndrome components.**

Posterior cranial fossa	Arachnoid cyst in the right pontocerebellar angle.
Haemangioma	Large, extensive, bilateral, several dermatomas, after radiation therapy in childhood.
Arterial abnormalities	Right internal carotid artery agenesis, left vertebral artery agenesis, persistent primitive maxillary artery, proximal aortic arch origin of the right ascending cervical artery, right posterior communicating artery aneurysm.
Cardiac and aorta	Ventricular septal defect with left to right shunt, right-sided aortic arch, coarctation in loco typico
Eye	Right eye bulb phthysis with optical nerve atrophy.

Pascual-Castroviejo in 1978 proposing the terminology of the cutaneous haemangioma vascular complex [3]. Large cervicofacial haemangiomas are associated with posterior cranial fossa abnormalities[4,5]. Haemangiomas in PHACE(S) syndrome show a 9:1 female: male ratio involve several cervicofacial segments [6]. Mulliken et Al. classified haemangiomas and vascular malformations in infants and children based on endothelial characteristics [7].

The vascular anomalies in this syndrome are highly complex [8,9,10]. We have seen all components of this syndrome associated also with right-sided aortic arch, aortic coarctation and ventricular septal defect (Table 1).

This conjunction of cardiac disease and large-vessel components failure shows possible involvement of the neural crest [11]. The lower rhombencephalic crest cells contribute to the heart and aortic wall media layer development, while more cranial crest cells contribute to the development of aortic arch vessels, carotid and vertebral arteries [12]. The timing of neural crest injury associated with persistence of branchial arteries and failure of carotid and vertebral arteries development may be focused on the period of the first eight weeks. Etchevers et Al.[1] showed that neural crest provides pericytes and smooth muscle cells to all blood vessels of the face and forbrain. The etiology of embryonic insult to the neural crest is still unknown.

Conclusions

PHACE syndrome is associated with a high incidence of wide spectrum of anomalies with persistence of fetal vascular circulation [13,14,15,16]. Neuroimaging like brain computed tomography, magnetic resonance, 3D-XRA digital subtraction angiography and echocardiography are recommended to search for structural cerebral defects, intra and extracranial vascular anomalies and persistence of cardiac defects in patients with large extensive facial haemangiomas.

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